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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/230,933	04/02/99	KLEINSCHMIDT J	4121-107

EXAMINER

CONNELLY

PM12/0203

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ART UNIT	PAPER NUMBER
1633	7

DATE MAILED: 12/03/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/230,929	Kleinschmidt, J. et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-13 is/are pending in the application.

Of the above, claim(s) 6-13 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-5 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Federal Republic of Germany, application number 196 31 357.0 on 08/02/96. It is noted, however, that applicant has not filed a photocopy of the application. A photocopy of the priority document is required since it was a PCT filing.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.371 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Applicant must state specifically: This application was filed under 35 U.S.C. 371, which was the National Stage of International Application No. PCT/DE97/01629, filed 07/30/97.

The WO patent documents, WO 96/11272 and wo 94/21808, in German have not been considered because they were not accompanied by an English translation of the German document.

Claims 6 -13 are objected to under 37 CFR 1.75 (c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, such as and/or, and cannot depend from any other multiple dependent claim. See MPEP 6.08.01 (n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claimed invention is to an adeno-associated viral vector (AAV) coding for a fusion polypeptide comprising any structural polypeptide from any papilloma virus and any non-transforming polypeptide encoded by any early papilloma virus gene.

In analyzing whether the written description requirement is met for genus claims, such as AAV comprising a nucleic acid coding for a fusion polypeptide, it is first determined whether a representative number of species has been described by their complete structure. The structural papilloma virus polypeptide delineated in the invention, is coded by L1-ORF or L2-ORF of a papilloma virus and by part thereof, of any origin and variant, while the early papilloma virus genes coding for non-transforming polypeptides disclosed species include E1, E2, E3, E4, E5, E6, E7-ORF, and by part thereof, also of any origin and variant. It is not readily apparent that the specification as filed would appraise one skilled in the art of a representative number of species to adequately describe the broad genus of non-transforming papilloma virus polypeptides

encompassed by the claims. The specification provides a limited number of papilloma virus non-transforming genes.

The specification asserts that the fusion polypeptide refers to the structural papilloma virus polypeptide and the non-transforming polypeptide coded by an early papilloma virus gene which would be present in any combination within the fusion polypeptide. The preferred fusion polypeptides comprises polypeptides coded by HPV 16L1-ORF and a polypeptide coded by HPV 16 E6-ORF and E7-ORF respectively, and polypeptide coded by HPV 18 L1-ORF and a polypeptide coded by HPV 18 E6-ORF and E7-ORF, respectively. The specification does not disclose the biological activity of any other papilloma virus ORFs such as to reasonably convey that the applicant was in possession of the claimed polypeptides and DNA thereof.

Therefore, it is concluded that the written description requirement is not satisfied for the claimed genus since one skilled in the art would not recognize what other early papilloma virus genes, and what other structural papilloma virus genes, would be included within the broad genus of derivatives encompassed by the claims.

Claims 1-5 are rejected under 35 U.S.C. 112 first paragraph, because the specification while being enabling for an AAV vector comprising a nucleic acid coding for a fusion polypeptide comprising a structural papilloma virus polypeptide and a non-transforming polypeptide coded by an early papilloma virus gene, wherein the fusion polypeptides comprise a polypeptide coded by HPV-16L1-ORF and a polypeptide coded by HPV 16 E6-ORF and E7-

ORF, and another fusion polypeptide coded by HPV 18 L1-ORF and polypeptide coded by HPV-18 E6-ORF and E7-ORF respectively, does not reasonably provide enablement for any AAV vector comprising any nucleic acid, coding for a fusion polypeptide comprising any structural protein of any papilloma virus and any non-transforming polypeptide coded by any early papilloma virus gene. The specification does not enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to an AAV vector encoding a nucleic acid which codes for a fusion protein comprising any structural protein of any papilloma virus and any non-transforming polypeptide coded by any early papilloma virus gene, and wherein the papilloma virus is an HPV or HPV 16, 18, 33, 35, and 45. Claims 4 and 5 are broadly drawn to an AAV vector encoding a nucleic acid coding for a fusion protein as per claims 1-3 but further regulated by any tissue-specific or tumor-specific promoter.

2. The in vitro examples and results on page 6 of the specification shows that applicant has been successful in preparing an HPV16 L1-E7 fusion polypeptide. The specification teaches generally, how the fusion polypeptide was obtained. Briefly, the L1-ORF of a genomic HPV16 clone was amplified by PCR reaction, after which the amplified DNA fragment was cleaved and inserted into the restriction site of the vector. The L1-ORF coded for an L1 in which the last 34 amino acids were deleted. In a similar fashion, the E7-ORF of HPV16 clone was also amplified by PCR reaction, after which the amplified DNA fragment was cleaved and inserted into the

restriction site of the above recited vector, encoding the shortened L1. Thus the L1-E7 fusion protein was obtained.

3. It is not readily apparent that one skilled in the art given applicant's disclosure alone, would be able to practice the invention over the scope claimed. In the instant situation, the claims embrace any structural papilloma virus gene of any origin fused with a gene coding for a non-transforming early papilloma virus protein of any origin. The specification gives specifics only for the fusions taught. It remains unclear that the state of the art regarding papilloma viruses at the time of the invention was such that one skilled in the art would have been able to routinely isolate any papilloma virus structural gene and or any non-transforming early papilloma virus encoding gene from any papilloma virus as broadly claimed. Such is considered to require an undue amount of experimentation in view of the lack of guidance provided in the specification as filed.

4. The quantity of experimentation required to practice the invention as claimed would require the identification of any and all structural genes of any papilloma virus, whether such papilloma viruses have been characterized at the level of the gene or not. Further, it would require characterization of early papilloma virus genes coding for non-transforming proteins. The artisan would have to screen and characterize innumerable papilloma virus genomes for such genes and with the intended functionality. One is also left to "trial and error" experimentation to choose the appropriate papilloma virus and genes thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Boursnell et al, 1992, in view of Bartlett et al, 1996.

Applicant claims an adeno-associated viral vector (AAV) having a nucleic acid coding for a fusion polypeptide comprising a structural papilloma virus polypeptide and a non-transforming polypeptide coded by an early papilloma virus gene. Applicant also claims that the nucleic acid of the AAV vector is under the control of a constitutive or inducible promoter, wherein the promoter is tissue specific or tumor specific. The papilloma virus claimed by applicant is a human papilloma virus (HPV) selected from the group consisting of HPV 16, 18, 33, 35 and 45.

Boursnell et al teaches the construction of a fusion polypeptide consisting of the genetic sequences encoding part or all of the proteins E6 and E7 from both HPV 16 and HPV 18 to form a single open reading frame (see page 9, lines 9-21). Boursnell et al further teaches that "for successful expression of foreign proteins by the recombinant virus vector the foreign genes must be placed under the control of a promoter sequence which is operable by the virus (see page 15, lines 21-24)". The vector may comprise one or more promoters which control the expression of the genetic sequences from one or more open reading frames (see page 16, lines 2-8). Finally, Boursnell et al teaches the recombinant virus vectors encoding human papilloma virus proteins 16, and 18(see page 1, lines 5-12).

Boursnell et al differ from the claimed invention in that they do not teach specifically the recombinant adeno-associated viral vector encoding HPVs.

It would have been prima facie obvious at the time the invention was made to utilize recombinant viral vectors for stable and efficient gene transduction and expression in mammalian cells since the prior art taught the transduction and expression of HPVs via recombinant viral vectors. Thus, there was an explicit teaching of utilizing recombinant viral vectors to infect and express HPV proteins in mammalian host cells (Boursnell et al, see abstract).

It would have been further obvious to utilize the recombinant adeno-associated viral vector(rAAV) taught by Bartlett et al, for stable and efficient integration of viral DNA into the host genome. Other advantages of rAAV delineated by Bartlett et al included, the absence of diseases associated with rAAV, the broad host range, the ability of rAAV to infect growth

arrested cells, and the ability of rAAV to carry non-viral regulatory sequences without interference from the viral genome (Bartlett et al, see page 77).

One would have been motivated to combine the teachings in the prior art as taught by Boursnell and Bartlett to recognize that recombinant viral vectors would be used to infect and express HPV proteins in mammalian host cells, and as such would be suitable for use as an immunotherapeutic or vaccine. One would be especially motivated to utilize the rAAV to infect and express HPV since it has been shown that rAAV possesses an extensive host range and is not associated with any diseases; features critical for vaccine therapy or immunotherapy.

There would have been a reasonable expectation of success because Boursnell et al demonstrated conclusively that the HPV fusion proteins were successfully expressed using a recombinant viral vector (see page 40-41, lines 27-2 respectively).

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

January 19, 2000

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1300
1600